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MICROFLUIDIC SURFACES

Technical field

The invention concerns a microfluidic device comprising a set of one or more, preferably more than 5, covered microchannel structures manufactured in the surface of a planar substrate made of inorganic or organic material, preferably plastics. The primary use is in analytical and preparative systems in which flow of an aqueous liquid transport one or more reagents or sample (analyte) from one part of the structure to another.

Technical background.

Microfluidic devices require that liquid flow easily pass through the channels and that non-specific adsorption of reagents and analytes, including proteins, nucleic acids, cells, cell particles, bacteria and viruses, should be as low as possible, i.e. insignificant for the analytical reactions to be carried out. The first feature relates to hydrophilicity.

One demand on hydrophilic properties of surfaces within microfluidic devices is that pure water must be capable of spontaneously penetrating the volume surrounded by the coated surface. In the most preferred cases this means that aqueous liquids should be able to spontaneously penetrate microchannel structures by capillary forces. This means that in going from [illegible] applied to the mouth of a microchannel) the hydrophilic property of the channel surface becomes of utmost importance. The flow properties will thus be improved by increasing surface hydrophilicity, i.e. lowering the water contact angle of the surface. From our experience, water contact angles around 20 degrees or lower may be needed to accomplish reliable passive fluid movement into the larger variants of the microformat structures. However, it is not simple to

manufacture surfaces which permanently have such low water contact angles. A tendency for a change in water contact angle during storage may, for instance, render it difficult to market microfluidic devices having standardised flow properties.

The situation is further complicated by the fact that most methods used to prepare surfaces with very low water contact angles do not reduce the tendency of the surfaces to non-specifically adsorb the reagents and sample constituents discussed above. Since the surface/volume ratio increases when going from a macroformat down to smaller formats, a surface's non-specific adsorption capacity relative the volume increases. Non-specific adsorption is therefore more critical in microformat devices than in larger devices and will increase inversely with format size.

There is a number of methods available for treating various surfaces to make them hydrophilic in order to reduce non-specific adsorption of various kinds of biomolecules, such as proteins and other biomaterials noted above. However, these methods generally do not concern the above-mentioned problem about balancing a reliable and reproducible liquid flow with a low non-specific adsorption when miniaturizing macroformats down into microformats. Compare for instance Elbert et al., (Annu. Rev. Mater. Sci. 26 (1996) 365-394).

In SE 9901100-9, filed 1999-03-24 we describe the production of highly hydrophilic surfaces that retain their hydrophilicity even after being in contact with aqueous liquids. An additional issue in SE 9901100-9 is to balance a permanent hydrophilicity with cell attachment properties.

Surfaces that have been rendered repelling for biopolymers in general by coating them with adducts between polyethylenimines and hydrophilic polymers have been described during the last decade (Brink et al (US 5,240,994), Bergström et al., US 5,250,613; Holmberg et al., J. Adhesion Sci. Technol. 7(6) (1993) 503-517; Bergström et al., Polymer Biomaterials, Eds

Cooper, Bamfors, Tsuruta, VSP (1995) 195-204; Holmberg et al., Mittal Festschrift, Eds Van Ooij, Anderson, VSP 1998, p 443-460; and Holmberg et al., Biopolymers at Interfaces, Dekker 1998 (Surfactant Science Series 75), 597-626). Attaching polyethylenimine to surfaces and subsequently attaching a polyethylenamine with a hydrophilic polymer have also been described (Kiss et al., Prog. Colloid Polym. Sci. 74 (1987), 113-119). These publications are scarce about the specific problems that are at hand in microfluidic devices having microchannel structures in which a liquid flow is transporting analytes and/or reagents reproducible through a microchannel sructure in one and the same direction.

Non-specific adsorption and/or electroendosmosis have been controlled in capillary electrophoresis by coating the inner surface of the capillary used with a hydrophilic layer, typically in form of a hydrophilic polymer (e.g. van Alstine et al US 4690749; Ekström & Arvidsson WO 9800709; and Bell et al., SPIE-Int. Soc. Opt. Eng. (1998) 3258 (Micro- and Nanofabricated Structures and Devices for Biomedical Environmental Applications) 134-140). Still other publications in this field are Hjerten, US 4680201 (poly methacrylamide); Karger et al., US 5840388 (polyvinyl alcohol (PVA)); Soane et al., US5858188 (acrylic microchannels). Capillary electrophoresis is a common name for separation techniques carried out in a narrow capillary utilizing an applied electric filed for separation of the analytes.

The invention

We have discovered that by properly attaching a hydrophilic non-ionic polymer to the surface of a microchannel structure surfaces that will enable both a reliable and reproducible transport of reagents and sample constituents in a liquid flow, and a sufficiently low non-specific adsorption.

Thus the invention is a microfluidic device comprising a set of one or more, preferably more than 5, covered microchannel structures manufactured in the surface of a planar substrate. By covered is meant that are essentially covered by some type

of lid thereby preventing evaporation of liquids. The characterizing feature is that the surface of at least a part of each microchannel structure exposes a firmly attached non-ionic hydrophilic polymer to the interior of the structure.

The hydrophilic polymers used in the invention should be neutral and inert towards the various reagents and chemicals that may be used in the microfluidic devices of the invention. Thus the typical hydrophilic polymers contain a plurality of neutral and nonchargeable hydrophilic groups selected among hydroxy, a polyethylene oxide groupings, amide that may be N-substituted etc. Typically the hydrophilic polymer is soluble in water when not bound to the surface of a microchannel structure.

The hydrophilic polymer groups are thus preferably selected among non-ionic polymers, such as polyethylene glycol, or more or less randomly distributed or block-distributed homo- and copolymers of lower alkylene oxides (C_{1-10}) or lower alkylene (C_{1-10}) bisepoxides in which the epoxide groups are linked together via a carbon chain comprising 2-10 sp^3-carbons. The carbon chain may at one or more positions be broken by an ether oxygen. Other suitable polymers are adducts of ethylene oxide, optionally in combination with higher alkylene oxides or bisepoxides, or tetrahydrofuran, with a dihydroxy or polyhydroxy compound, such as glycerol and pentaerythritol as well as polysaccharides, such as dextran and starch, with cellulose ethers such as methyl cellulose, methyl hydroxy propyl cellulose, or ethyl hydroxy ethyl cellulose; polyvinyl alcohol being other suitable hydrophilic polymers. Included are potentially also various kinds of polyhydroxy polymers, [illegible] vinyl ether) polymers and polymers obtained by polymerisation of epichlorohydrine, glycidol and similar bifunctionally reactive monomers giving polyhydroxy polymers. Other polymers of interest are polyvinylpyrrolidone polyacrylamides, polymethacrylamides etc. The hydrophilic polymer groups, when not bound to the polyamine skeleton are preferably water-soluble, and their molecular weight is within the range from

about 400 to about 200,000, preferably from about 1,000 to about 100,000.

The preferred hydrophilic groups comprise polyethylene oxide parts and have preferred molecular weights within limits just given.

The hydrophilic polymer may have the same structure as described for the extenders defined in Berg et al (WO 9833572) which is hereby incorporated by reference. In contrast to Berg et al there is no imperative need for the presence of an affinity ligand on the hydrophilic polymer used in the present invention.

The hydrophilic polymer may be attached to the surface of the microchannel structure via a polymer skeleton that in turn is attached to the substrate surface via multipoint attachment.

The attachment of the hydrophilic polymer to the polymer skeleton or directly to the substrate surface is preferably covalent. One or more positions in the hydrophilic polymer may be utilized for attachment. In order to make the hydrophilic polymer flexible the number of attachment points should be as low as possible, for instance one, two or three positions per polymer molecule, and then also involving terminal positions. For straight chain polymers, such as poly lower alkylene oxide chains, for instance polyethylene oxide chains, the number of attachment points is typically one or two, with preference for one.

Depending on the position of a coated surface part within a structure, the hydrophilic polymer may carry an immobilized reactant (often called ligand when affinity reactions are concerned). Depending on the particular use of a microchannel structure such reactants can be so called affinity reactants that are used to catch the analyte or an added reactant or a contaminant present in the sample. This also includes immobilized enzymes. When present in a microchannel

structures, this kind of reactants are preferably present in reaction chambers/cavities.

The polymer skeleton is in the preferred variants of the invention a polyamine , i.e. a polymer containing two or more primary, secondary or tertiary amine groups or quaternary ammonium groups. The preferred polyamines are polyalkylenimines, i.e. polymers in which amine groups are interlinked by alkylene chains, for instance C_{1-6} alkylene chains. The alkylene chains may carry neutral hydrophilic groups, for instance hydroxy (HO) or poly (including oligo) lower alkylene oxy groups [-O-$((C_2H_4)_nO)_mH$ where n is 1-5 and m may be from 1 and upwards for instance ≤ 100 or ≤ 50)], amide groups, acyl, acyloxy, lower alkyl (for instance C_{1-5}) and other neutral groups and/or groups that are unreactive under the conditions to be applied in the microfluidic device.

The preferred molecular weight of the skeleton including polyamine skeletons is within the range of 10,000-3,000,000, preferably about 50,000-2,000,000. The structure of the skeleton can be linear, branched, hyperbranched or dendritic. The preferred polyamine skeleton is polyethylenimine, a compound that is achievable e.g. by polymerizing ethylene imine, usually giving hyperbranched chains.

The introduction of the non-ionic hydrophilic polymer groups may be done according to principles well-known in the field for instance by directly attaching the hydrophilic polymer to the substrate surface or via the kind of skeleton discussed above. The adduct between the skeleton and the hydrophilic [illegible] the surface or (ii) on the surface by first attaching the skeleton and then the hydrophilic polymer, for instance by (a) grafting preprepared hydrophilic polymers or (b) graft polymerisation of corresponding polymerisable monomers.

The skeleton may be stabilized to the underlying surfaces via covalent bonds, electrostatic interaction etc and/or by cross-linking in step or afterwards. A polyamine skeleton, for

instance, may be attached covalently by reacting its amine functions with amine reactive groups that are present on the uncoated substrate surface.

It is important that the surface to be coated according to the invention has a chemical composition promoting adherence of the inventive coat. This means that groups enabling stable interaction between the hydrophilic polymer and the surface and between the skeleton and the surface have to be present on the nude substrate surface. With respect to attachment of skeletons of the polyionic type, for instance a polyamine, this means that the nude substrate surface should carry groups that are polar and/or electrically chargeable. Cationic skeletons, for instance polyamines, require that negatively chargeable groups or groups otherwise capable of binding to amine groups, typically hydrophilic, are exposed on the surface. Polar and/or chargeable groups may easily be introduced on plastics surfaces, for instance by treatment with O_2-containing plasmas, by oxidation with permanaganate or bichromate in concentrated sulphuric acid, by coating with polymers containing these type of groups etc, i.e. by techniques well-known in the scientific and patent literature. The plastics surface as such may also contain this kind of groups without any pretreatment, i.e. by being obtained from polymerisation of monomers either carrying the above-mentioned type of groups or groups that subsequent to polymerisation easily can be transformed to such groups. This includes also monomers carrying groups that are easily transformable to groups permitting attachment of the skeleton or a hydrophilic polymer. In certain kind of skeletons, polar groups, such as the amine and quaternary ammonium groups of polyamines are linked together by relatively hydrophobic groups. Illustrative examples of this kind of hydrophobic groups are pure alkylene chains comprising three or four or more carbon atoms. In these cases one can envisage that it might be possible to attach these skeletons also by hydrophobic adsorption forces.

In order to maintain good liquid flow properties and reliable transport of liquid, reagents, sample constituents and the

like the water contact angle should be as low as possible. The optimal water contact angle depends on the analysees and reactions to be carried out in the microchannel structure, dimensions of the microchannels and chambers of the structures, composition and surface tension of liquids used, etc. As a rule of thumb, the inventive coat should be selected to provide a water contact angle that is ≤ 30°, such as ≤ 25° or ≤ 20°. So far the most superior surfaces have been those based on adducts between polyethylene imine and polyethylene glycol with monosite (mono group terminal) attachment of the hydrophilic polymer to the polyethylene imine skeleton. The best mode to date of this preferred variant is given in the experimental part (example 1).

The thickness of the hydrated coat provided by the hydrophilic non-ionic polymers should be ≤ 50 %, for instance ≤ 20 %_of the smallest distance between two opposing sides of a part of the microchannel structure comprising the surface coated according to the invention. This typically means that optimal thicknesses will be within the interval 0.1-1000 nm, for instance 1-100 nm, with the provision that in at least the channels for liquid transport the coat is not blocking liquid flow .

Structures in the microfluidic device.

The microfluidic device may be disc-formed of various geometries with the round disc being the preferred variant (CD-form).

In the round form the microchannel structures may be arranged radially from an inlet port near the centre of the disc application area radially towards the periphery of the disc. In this variant the most practical ways of driving the flow is by capillary action, centripetal force (spinning the disc) and/or hydrodynamically.

Each microchannel structure comprises one or more channels and/or one or more cavities in the microformat. Different

parts of a structure may have different discrete functions. Thus there may be one or more parts that function as (a) application chamber/cavity/area (b) conduit for liquid transport, (c) reaction chamber/cavity, (d) volume defining unit, (e) mixing chamber/cavity, (f) chamber for separating components in the sample, for instance by capillary electrophoresis, chromatography and the like (g) detection chamber/cavity, (h) waste conduit/chamber/cavity etc. According to the invention at least one these parts may have the inventive coat on its surface.

When the structure is used, necessary reagents and/or sample including the analyte, if not incorporated in advance in a certain part of the structure, are applied to an application area and transported downstream in the structure by an applied liquid flow. The liquid flow may be driven by capillary forces, an/or centripetal force, pressure differences applied externally over a microchannel structure and also other non-electrokinetic forces that are externally applied and cause transport of the liquid and the analytes and reagents in the same direction. Forces that may be utilized for the transport include also electroendoosmosis. The liquid flow is thus transporting reagents and analytes and other constituents from the application area/cavity/chamber into a sequence comprising a particular order of preselected parts (b)-(h). The liquid flow may be paused when a reagent and/or analyte have reached a preselected part in which they are subjected to a certain procedure, for instance capillary electrophoresis in a separation part, a reaction in a reaction part, detection in a detection part etc.

Analytical and preparative methods as discussed below utilizing the microfluidic device of the invention with transport of liquid, reagents and analytes as described in the preceding paragraph constitute a separate aspect of the invention.

Microformat means that at least one liquid conduit in the structure has a depth and/or width that is in the microformat

range, i.e. < 10^3 µm, preferably < 10^2 µm. Each microchannel structure extends in a common plane of the planar substrate material. In addition there may be extensions in other directions, primarily perpendicular to the common plane. Such other extensions may function as sample or liquid application areas or connections to other microchannel structures that are not located in the common plane, for instance.

More particularly in the channels of a microchannel structure the distance between two opposite walls is ≤ 1000 µm, such as ≤ 100 µm, or even ≤ 10 µm, such as ≤ 1 µm. The structures may also contain one or more chambers connected to the channels and having volumes being ≤ 500 µl, such as ≤ 100 µl and even ≤ 10 µl such as ≤ 1 µl. The depths of the chambers may typically be in the interval ≤ 1000 µm such as ≤ 100 µm such as ≤ 10 µm or even ≥ 1 µm. The lower limit is always significantly greater than the largest of the reagents used. The lower limit is typically in the range 0.1-0.01 µm for devices that are to be delivered in dry form.

It is believed that the preferred variants of the inventive microfluidic devices will be delivered to the customer in a dried state. The surfaces of the microchannel structures of the device therefore should have a hydrophilicity sufficient to permit the aqueous liquid to be used to penetrate the

There may be conduits enabling liquid communication between individual microchannel structures within a set.

Material in the microfluidic device.

Typically the plastic material to be coated according to the invention may have been obtained by polymerisation of monomers comprising unsaturation such as in carbon-carbon double bounds or carbon-carbon-triple bonds.

The monomers may, for instance, be selected from mono-, di and poly/oligo-unsaturated compounds, e.g. vinyl compounds and other compounds containing unsaturation. Illustrative monomers are:

(i) alkenes/alkadienes (such as ethylene, butadiene, propylene and including substituted forms such as vinyl ethers), cycloalkenes, polyfluorovinyl hydrocarbons (for instance tetrafluoroethylene), alkene-containing acids, esters, amides, nitriles etc for instance various methacryl/acryl compounds; and

(ii) vinyl aryl compounds (such as mono-, di- and trivinyl benzenes) that optionally may be substituted with for instance lower alkyl groups (C1-6) etc.

Another type of plastics are based on condensation polymers in which the monomers are selected from compounds exhibiting two or more groups selected among amino, hydroxy, carboxy etc groups. Particularly emphasised monomers are polyamino monomers, polycarboxy monomers (including corresponding reactive halides, esters and anhydrides), poly hydroxy monomers, amino-carboxy monomers, amino-hydroxy monomers and hydroxy-carboxy monomers, in which poly stands for two, three or more functional groups. Polyfunctional compounds include compounds having a functional group that is reactive twice, for instance carbonic acid or formaldehyde. The plastics contemplated are typically polycarbonates, polyamides, polyamines, polyethers etc. Polyethers include the corresponding silicon analogues, such as silicon rubber.

The polymers of the plastics may be in cross-linked form.

The plastics may be a mixture of two or more different polymer(s)/copolymer(s).

Particularly interesting plastics are those that have a non-significant fluorescence for excitation wavelengths in the interval 200-800 nm and emission wavelengths in the interval 400-900 nm. By non-significant fluorescence is meant that the fluorescence intensity in the above-given emission wavelength

interval should be below 50 % of the fluorescence intensity for a reference plastics (= a polycarbonate of bisphenol A without fluorescent additives). In fact it does not harm in case the fluorescence intensity of the plastics is even lower, such as < 30 % or < 15 %, such as < 5 % or < 1 %, of the fluorescence intensity of the reference plastics. Typical plastics having an acceptable fluorescence are based on polymers of aliphatic monomers containing polymerizable carbon-carbon double bonds, such as polymers of cykloalkenes (e.g. norbornene och substituterade norbornenes), ethylene, propylenes etc, as well as other non-aromatic polymers of high purity, e.g. certain grades of polymethylmethacrylate.

Applications in which the inventive microfluidic device can be used.

Typical analytical systems in which the microfluidic systems described herein may comprise as the main steps one or more of (a) sample preparation, (b) assay reactions and (c) detection. Sample preparation means the preparation of a sample in order to make it suitable for the assay reactions and/or for the detection of a certain activity or molecular entity. This may for example mean that substances interfering with the assay reactions and/or detection is removed or otherwise neutralized, that substances are amplified and/or derivatized etc. Typical examples are amplifying one or more nucleic acid sequences in a sample, for instance by polymerase chain reaction (PCR), removing of species cross-reacting with an analyte in assays involving affinity reactions etc. Typical assay reactions are reactions involving cells, affinity reactions, for instance biospecific affinity including immune [illegible] precipitation reactions, pure chemical reactions involving formation or breaking up of covalent bonds and many others. The detection reaction may involve fluorometry, chemiluminometry, mass spectrometry, nephelometry, turbidometry etc. The applicable analytical systems may thus comprise affinity assays, such as immune assays, hybridisation assays, cell biology assays, mutation detection, genome characterisation, enzyme assays, screening assays for finding

new affinity pairs etc. Methods for the analysis of sample content of proteins, nucleic acids, carbohydrates, lipids and other molecules with particular emphasis of other bio-organic molecules are also included.

The microfluidic device of the present invention may also find use for the set up of libraries of compounds including synthetic peptide and oligonucleotide libraries, for instance by solid phase synthesis. The synthesis of so called combinatorial libraries of compounds is also included.

The invention will now be described with reference to non-limitative experiments that function as proof of principle.

EXPERIMENTAL PART

1. Synthesis of PEG-PEI adduct

0.43 g of polyethylenimine (Polymin SN from BASF, Germany) was dissolved in 45 ml of 50 mM sodium borate buffer (pH 9.5) at 45°C. 5 g of the glycidyl ether of monomethoxy polyethylene glycol (Mw 5 000) was added during stirring and the mixture was stirred for 3 h at 45°C.

2. Surface treatment

A polycarbonate CD disc (polycarbonate of Bisphenol A, Macrolon DP-1265, Bayer AG, Germany) with a recessed microchannel pattern was placed in a plasma reactor (Plasma Science PE50, BOC Coating Technology, USA) and treated with an oxygen plasma at 5 sccm gas flow and 500 W RF power for 10 min. After venting the reactor, the disc was immersed in a [illegible] solution of the PEG-PEI adduct in borate buffer pH 9.5 for 1 h. The disc was then rinsed with distilled water, blow-dry with nitrogen and the water contact angle (sessile drop) was measured on a Ramé-Hart manual goniometer bench. The average of six equilibrium measurements (three droplets) was 24 degrees. An XPS spectrum of the treated surface gave the following molar elemental composition: 73.2% C, 3.7 % N, 23.1% O, showing that the surface was essentially covered by the adsorbed PEG-PEI adduct.

3. Capillary wetting

Another polycarbonate CD disc of the same material as above with a recessed microchannel pattern was treated as in example 2. It was then covered with a thin silicone rubber lid, with a hole placed over a microchannel. When a droplet of water was placed in the hole with a micropipette, the water was drawn in by capillary forces and penetrated the entire accessible channel system.

4. Comparative examples of surface treatments

a) A polycarbonate disc of the same material as above with a recessed microchannel pattern was dipped into a 0.5% water solution of phenyl dextran (degree of substitution: 0.2 per monosacharide unit of dectran, Mw 40 000) for 1 h. After water rinsing, the disc was blown dry with nitrogen. The water contact angle was 30 degrees. When a silicone rubber lid was placed over the disc with a hole over a channel, the droplet was not spontaneously drawn in. When a vacuum was applied to the channel through another hole in the lid, the droplet could however be introduced by suction.

b) A polycarbonate disc of the same material as above with a recessed microchannel pattern was immersed over night in a 1 % water solution of a polyethylene glycol ※ polypropylene glycol ※ polyethylene glycol triblock copolymer (Pluronic F108 from BASF). After water rinsing the disc was blown dry with nitrogen. The water contact angle was 60 degrees. When a silicone rubber lid was placed over the disc with a hole over a channel, the droplet was not spontaneously drawn in. When a vacuum was applied to the channel through another hole in the lid, the droplet could however be introduced by suction.

C L A I M S

1. A microfluidic device comprising a set of one or more, preferably more than 5, covered microchannel structures manufactured in the surface of a planar substrate, characterized in that the surface of a part of at least one of the microchannel structures is covered with a coat exposing a non-ionic hydrophilic polymer that preferably is attached covalently directly to the surface or to a polymer skeleton that is attached to the surface.

2. The microfluidic device of claim 1, **characterized** in that the surface of the planar substrate is made of plastics.

3. The microfluidic device according to anyone of claims 1-2, **characterized** in that the non-ionic hydrophilic polymer is attached to the polymer skeleton that is attached to the surface, said skeleton preferably being branched and/or preferably being a polyamine.

4. The microfluidic device according to anyone of claims 1-4, **characterized** in that the substrate surface without the coat is made of plastics and that said surface part without coat is hydrophilized by plasma treatment or by an oxidation agent in order to introduce functional groups that allow for a subsequent attachment of the coat onto said surface part.

5. The microfluidic device according to anyone of claims 1-4, **characterized** in that the hydrophilic non-ionic polymer comprises one or more blocks of polyoxyethylene chains, with [illegible] covalently attached at one of its ends and possibly having the remaining hydroxy group etherified.

6. The microfluidic device according to anyone of claims 1-6, **characterized** in that the hydrophilic non-ionic polymer is a polyethylene glycol, preferably a monoalkoxy such as monomethoxy variant, which is attached to said surface part [illegible]

7. The microfluidic device according to anyone of claims 1-6, **characterized** in that the hydrophilic non-ionic polymer is attached to said surface part or to said polymer skeleton via one-point attachment, preferably covalently.

8. The microfluidic device according to anyone of claims 2-7, **characterized** in that the plastics has a non-significant fluorescence for excitation wavelengths in the interval 200-800 nm and emission wavelengths in the interval 400-900 nm.

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A B S T R A C T

A microfluidic device comprising a set of one or more, preferably more than 5, covered microchannel structures manufactured in the surface of a planar substrate. The device is characterized in that the surface of a part of at least one of the microchannel structures is covered with a coat exposing a non-ionic hydrophilic polymer that preferably is attached covalently directly to the surface or to a polymer skeleton that is attached to the surface